



NTP
National Toxicology Program

Research Concept: Ethylene Glycol 2-Ethylhexyl Ether

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NIEHS/NTP

NTP Board of Scientific Counselors Meeting

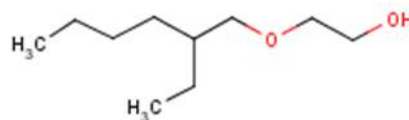
November 20-21, 2008





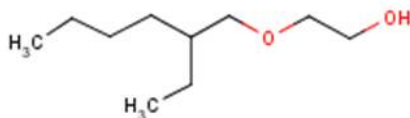
Production, Use, and Exposure

- Ethylene glycol 2-ethylhexyl ether (EGEHE) was nominated by the NIEHS.
- EGEHE, a solvent, is used in a wide variety of products that include:
 - coatings, paints, sealants, cleaners.
- EGEHE production has been increasing (1990, 1994, 1998) and reported to be > 1-10 million pounds in the U.S. (EPA 2002).
- Occupational or non-occupational exposure may be through inhalation or dermal routes (no exposure data are available).





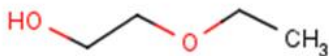
Ethylene Glycol Ethers



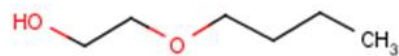
Ethylene glycol 2-ethylhexyl ether
(EGEHE)



**Ethylene glycol methyl ether
(EGME)**
2-Methoxyethanol



**Ethylene glycol ethyl ether
(EGEE)**
2-Ethoxyethanol

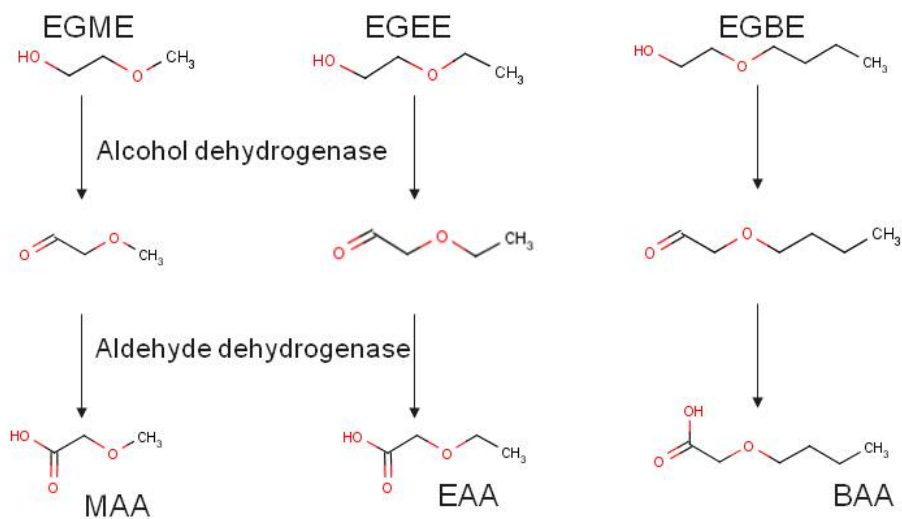


**Ethylene glycol butyl ether
(EGBE)**
2-Butoxyethanol



Ethylene Glycol Ether Metabolism

- EGEHE metabolism is unknown, but may be similar to the other ethylene glycol ethers:





Toxicity Overview of Ethylene Glycol Ethers

- EGME and EGEE are known testicular toxicants (EGME > EGEE).
 - Seminiferous epithelium degeneration
 - Depletion of sperm and reduced fertility
- EGME and EGEE are developmental toxicants.
 - Exencephaly, effects on digit morphogenesis, various other soft tissue and skeletal malformations
- EGME, EGEE, EGBE are hematotoxic.
 - EGME toxic to leukocytes and erythrocytes; EGBE toxic to erythrocytes.
 - Lesions in thymus, bone marrow, spleen.



EGEHE Toxicity Data

- Low acute toxicity:
 - oral LD50 for rats 7832/5149 mg/kg (fasted/fed).
 - oral LD50 for mice 7308/3898 mg/kg.
 - dermal LD50 for rabbits 2584 mg/kg.
- EGEHE exposure via gavage (6 wks, 5d/wk) in male rats at 1/2, 1/4, 1/8 the fasted LD50. Findings:
 - High mortality in the top dose within 4 days of dosing.
 - Degenerating spermatozoa in epididymides (2/10) at high dose (no testis atrophy noted).
 - Mixed results in hematology of two remaining dose groups.
 - Increased liver weights in remaining dose groups, splenic congestion (high and mid dose).



Carcinogenicity of EGBE via inhalation (NTP)

- EGBE chronic bioassay via inhalation (NTP).
 - Some evidence of carcinogenicity in male and female mice.
 - Male mice: Increased hemangiosarcomas, and uncertain findings of hepatocellular carcinoma and forestomach squamous cell papilloma
 - Female mice: Increased forestomach squamous cell papilloma and carcinomas
 - No evidence (male) or equivocal evidence (female) of carcinogenicity in rats.
 - Female mice: Benign or malignant pheochromocytoma
 - IARC (2006) concluded that EGBE was not classifiable as to its carcinogenicity in humans (Group 3).
 - Limited evidence in experimental animals; inadequate evidence in humans.



EGEHE Key Issues

- EGEHE is a high production chemical and it is structurally related to other Ethylene Glycol Ethers that adversely affect reproduction, development, and hematology.
- EGEHE metabolism is not characterized and may yield known toxic metabolites or unknown metabolites.
- EGEHE toxicity after *in utero* or chronic exposure is not known - one subchronic study in male rats.



Proposed Approach

1. Characterize the ADME of EGEHE in order to:
 - Identify possible known toxic ethylene glycol ether metabolites.
 - Evaluate different routes of exposure.
 - Identify potential ADME differences between males and females.

2. Evaluate toxicity from subchronic EGEHE exposure:
 - Subchronic studies to characterize toxicity.
 - Attention to testicular and hematotoxic effects.
 - *In utero* exposure to evaluate developmental toxicity (teratology).
 - *In vitro* assays to evaluate genetic toxicity.

3. Studies to evaluate immune, reproductive, and chronic toxicity.



Significance

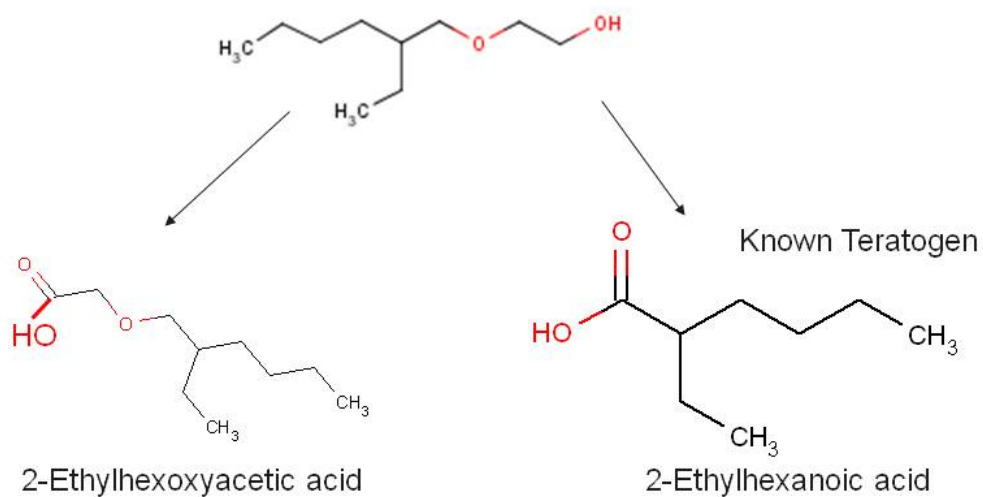
- EGEHE is a compound that is increasing in production, has an unknown toxicity profile, and is structurally related to other known toxic ethylene glycol ethers.
- Characterizing the ADME and toxicity of EGEHE would provide data for risk assessment by regulatory agencies and information for the general public.



Questions and Comments



Meteor Report





Ethylene Glycol EthylHexyl Ether

- Oral LD50 (male rats and mice):
 - 9 EGE's: acute toxicity increased as MW increased; toxicity for mice \geq rats.
 - EGEHE was 1.5 times more toxic in fed than fasted animals.
 - EGEHE LD50 (fed) for rats: 29.6 mM/kg (5149 mg/kg); mice: 22.4 mM/kg (3898 mg/kg).
 - Dermal LD50: EGEHE dermal LD50: 14.85 mM/kg (2584 mg/kg).

- 6 week intermediate study (male rat only):
 - Doses 1/2, 1/4, 1/8 the fasted LD50; EGEHE: 22 mM/kg (3828 mg/kg)*, 11 mM/kg (1914 mg/kg), 5.5 mM/kg (957 mg/kg); dosed 29-33 days via gavage over a 44 day period.
 - EGEHE (all animals died in top dose):
 - Enlarged liver, splenic congestion (high and mid dose).
 - Diffuse hemorrhage of thymus in high dose.
 - Degenerating spermatozoa in epididymides (2/10) at high dose (no testis atrophy noted).
 - Reduced hemoglobin in mid and low dose; no effect on erythrocytes; decreased glucose in mid dose; increased WBC at low dose.



Comparative toxicities

<i>Toxicity</i>	<i>Ranking</i>
Testicular	EGME > EGEE
Development	EGME > EGEE
Erythrocyte	EGBE > EGEE > EGME
Leukocyte	EGME > EGEE